

**U.S.S.N 09/887,281**  
**BANERJEE *et al.***  
**AMENDMENT**

B' cont. instrument, selectively removes large droplets from the mist by impaction.  
Thus, the mist inhaled into the lung contains fine aerosol droplets.

Please replace the paragraph on page 8, lines 23-29, with the following paragraph:

B<sup>2</sup> As used herein, the stability of a composition provided herein refers to the length of time at a given temperature that is greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient, *e.g.*, formoterol, is present in the composition. Thus, for example, a composition that is stable for 30 days at 25 °C would have greater than 80%, 85%, 90% or 95% of the initial amount of active ingredient present in the composition at 30 days following storage at 25 °C.

Please replace the paragraph beginning on page 8, line 30, through the paragraph on page 10, line 4, with the following paragraph:

B<sup>3</sup> As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethyl-benzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts

U.S.S.N 09/887,281

BANERJEE *et al.*

AMENDMENT

*B3 cont*

of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula  $C=C(OR)$  where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula  $C=C(OC(O)R)$  where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecule, preferably 1 to about 100, more preferably 1 to about 10, most preferably one to about 2, 3 or 4, solvent or water molecules. Formoterol salts and hydrates are used in certain embodiments herein.

Please replace the paragraph on page 14, lines 8-16, with the following paragraph:

*B4*

In one embodiment, the  $\beta_2$ -adrenoreceptor agonist is formoterol, or a pharmaceutically acceptable derivative thereof. In other embodiments, the formoterol for use in the compositions provided herein is formoterol fumarate. Formoterol refers to 2-hydroxy-5-(((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide; or a stereoisomer thereof. The term formoterol also refers herein to the single enantiomers 2-hydroxy-5-(((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-(((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)-amino)ethyl)formanilide.

Please replace the paragraph beginning on page 16, line 8, through the paragraph on page 17, line 20, with the following paragraph:

B<sup>5</sup>

In other of the above embodiments, the compositions further contain a buffer, including, but not limited to, citric acid/phosphate, acetate, barbital, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), TRIZMA® (tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid), TRICINE (N-tris(hydroxymethyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanesulfonic acid)), TAPS (N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid), AMPD (2-amino-2-methyl-1,3-propanediol), and/or any other buffers known to those of skill in the art. In one embodiment, the buffer is citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer. In another embodiment, the buffer is a citrate buffer (citric acid/sodium citrate). The buffer concentration

B<sup>5</sup> cont  
has been found herein to affect the stability of the composition. Buffer concentrations for use herein include from about 0 or 0.01 mM to about 150 mM, or about 1 mM to about 20 mM. In one embodiment, the buffer concentration is about 5 mM. In another embodiment, the buffer concentration is about 1 mM to about 50 mM, or about 20 mM. The kinetic-pH profile of formoterol is dependent on buffer concentration. At low and approximately neutral conditions, increasing the buffer concentration from 5 mM to 20 mM increased the rate constant of decomposition significantly. However, no noticeable differences in rate constant were observed in the pH region of about 4.5 to about 5.5 with increasing buffer concentration from 5 mM to 20 mM. The particular buffer and buffer concentration of a given composition for long term storage provided herein may be determined empirically using standard stability assays well known to those of skill in the art (see, *e.g.*, the Examples).

Please replace the paragraph beginning on page 18, lines 1-25, with the following paragraph:

B<sup>6</sup>  
In embodiments where the pharmacologically suitable fluid is a saline solution, tonicity adjusting agents may be added to provide the desired ionic strength. Tonicity adjusting agents for use herein include those which display no or only negligible pharmacological activity after administration. Both inorganic and organic tonicity adjusting agents may be used in the compositions provided herein. Tonicity adjusting agents include, but are not limited to, ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide,

**U.S.S.N 09/887,281**  
**BANERJEE *et al.***  
**AMENDMENT**

B<sup>6</sup> cont  
potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine and zinc sulfate. In certain embodiments, the tonicity adjusting agent is sodium chloride, which is present at a concentration of from about 0 mg/mL to about 10, 15 or 20 mg/mL. In further embodiments, the compositions contain sodium chloride at a concentration of from about 0 mg/mL to about 7.5 mg/mL. In another embodiment, the compositions contain sodium chloride at a concentration of 0 mg/mL, 1.5 mg/mL, 6.8 mg/mL or 7.5 mg/mL. In these embodiments, the pharmacologically suitable fluid is aqueous saline.

Please replace the paragraph on page 22, lines 6-8, with the following paragraph:

B<sup>7</sup>  
Standard physiological, pharmacological and biochemical procedures are available for testing the compositions provided herein to identify those that possess bronchodilatory activity.

Please replace the paragraph on page 25, lines 9-16, with the following paragraph:

B<sup>8</sup>  
Prophylactic therapeutics for use in combination therapy herein include steroidal anti-inflammatory agents, including, but not limited to, beclomethasone dipropionate (BDP), beclomethasone monopropionate (BMP), flunisolide, triamcinolone acetonide, dexamethasone, tipredane, ciclesonid, rofleponide, mometasone, mometasone furoate (Asmanex<sup>®</sup> Twisthaler<sup>™</sup>, Shering-Plough Corporation, Kenilworth, NJ), RPR 106541, having the formula